UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,954	06/25/2001	Hubert Jan Jozef Loozen	O/98414-US	9900

27624 7590 09/11/2006

AKZO NOBEL INC.
INTELLECTUAL PROPERTY DEPARTMENT
7 LIVINGSTONE AVENUE
DOBBS FERRY, NY 10522-3408

EXAMINER	
COTTON, ABIGAIL MANDA	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,954	LOOZEN ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2006 and 13 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,8,13,14 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7,8,13,14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 13, 2006, has been entered.

Claims 1-2, 4, 7-8, 13-14 and 16 are pending in the application and are being examined on the merits herein.

The indication of allowability of dependent claims 2, 4, 14 and 16 as set forth in the Office Action mailed on November 14, 2005, is being withdrawn upon further consideration of the claims.

Applicants' arguments regarding the rejections of the claims over the prior art have been fully considered, but have not been found to be persuasive. The claims are rejected as set forth below.

Claim Objections

Claims 2 and 14 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. In particular, claims 2 and 14 recite that the sidechain R_{11} may take the form of the following structure:

which comprises a linear chain having a length of 3 carbon atoms that is attached to a cyclopropyl group. In contrast, claims 1 and 13, from which claims 2 and 14 depend, specify that R_{11} is a hydrocarbon group "comprising one single linear chain having a length of from 5 to 6 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton." Accordingly, claims 2 and 14 fail to further limit claims 1 and 13 because they recite a sidechain having a linear chain with a length of only 3 carbon atoms, instead of the 5 or 6 as required by claims 1 and 13.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4, 7, 13-14 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is not clear what is meant by the recitation that R_{11} is a hydrocarbon group "comprising one single linear chain having a length of from 5 to 6 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton," as recited for example in claims 1 and 13. The recitation is unclear because while it appears to specify that the sidechain must comprise at least one single linear chain having a length of 5 to 6 carbon atoms, claims 2 and 14 depending from claims 1 and 13 recite that a suitable sidechain includes compound 4 having the following structure:

Thus, the claims recite that a suitable sidechain includes a structure comprising a linear chain having a length of only 3 carbon atoms that is attached to a cyclopropyl group. Thus, the metes and bounds of the claims are not clear, because it is not clear how one is supposed to count the number of carbon atoms in the sidechain to determine the number of carbon atoms in the "single linear chain," and thus to

determine what compounds qualify as meeting the limitations of the steroid compound as recited in claim 1 having a group R_{11} with a linear chain having a length of from 5 to 6 carbon atoms. Appropriate correction and/or clarification is required.

In the interests of compact prosecution and for the purposes of applying prior art, the claims are being interpreted to mean that R_{11} is a hydrocarbon group having a single linear chain having 5 or 6 carbon atoms as the longest chain, and thus the structure 4 as recited in claims 2 and 14 is considered to be outside the scope of the claims (see objection to claims 2 and 14 above for failing to further limit the claims from which they depend.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4, 7-8, 13-14 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article entitled "Steroidal Affinity labels of the Estrogen Receptor.

3. Estradiol 11Beta-n-Alkyl Derivatives Bearing a Terminal Electrophilic Group: Antiestrogenic and Cytotoxic Properties" by Lobaccaro et al, 1997 (of record)

Lobaccaro et al. teaches the development of a new series of steroidal affinity labels of the estrogen receptor, including 11Beta-ethyl (C_2), 11Beta-butyl (C_4) and 11Beta-decyl (C_{10}) derivatives of estradiol (see abstract, in particular.) Lobaccaro et al. teaches the synthesis of compounds having the formula I wherein R11 is butene or ethene (see compounds 5a-5B, Scheme 1 on page 2218, in particular) and teaches testing of the binding of the butene derivative of estradiol 5b and its binding to the estrogen receptor, as well as its activity as an estrogen agonist (see Tables 1 and 2, in particular.) Lobaccaro et al. also refers to the compound 5b as being "estrogenic," i.e., and estrogen agonist (see paragraph bridging pages 2221-2222, in particular.) Lobaccaro et al. also generally concludes that for estradiol 11Beta-substituted derivatives, the size of the 11beta alkyl side chain is what affects the estrogenic vs. antiestrogenic activity, rather than the size of the whole substituent or the type of electrophillic group substituted on the side chain (see page 2223, first full paragraph, in particular.) Lobaccaro et al. teaches that the compounds having affinity for the estrogen receptor may have use in the treatment of estrogen receptor-containing mammary tumors (see paragraph bridging left and right hand columns, page 2223, in particular), and thus teaches the use of compounds that bind the estrogen receptor in a pharmaceutical composition or for pharmaceutical treatment.

Lobaccaro et al. does not specifically teach the estrogenic compound having the group R_{11} that is a hydrocarbon group and that has a single linear chain having a length of from 5 to 6 carbon atoms as the longest chain on carbon atom no. 11, as recited in claims 1, 8, and 13.

However, as the compound 5b of Lobaccaro et al. differs from the instantly recited compounds by only a methylene or ethylene group, that is, Lobaccaro teaches a C4 compound whereas the instant compounds are C5 or C6 compounds, it is considered that the instantly claimed compounds are homologous to the compound of Lobaccaro et al, and thus are expected to have similar properties to the compound as taught by Lobaccaro et al, such as estrogenic activity. Thus it is considered that one of ordinary skill in the art would have found it obvious to provide the C5 or C6 homologs of the Lobaccaro et al. C4 compound, with the expectation of providing a compound with similar properties. See *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977.)

Furthermore, as Lobaccaro et al. teaches that the length of the 11beta alkyl side chain can effect the estrogenic/antiestrogenic activity, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of length of the 11beta alkyl side chain of the compound, according to the guidance provided by Lobaccaro et al, to provide a composition having desired properties. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or

workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, the pharmaceutical composition of claim 1, and the steroid compound of claim 13 are considered to be obvious over the teachings of Lobaccaro et al. Regarding the recitation the compound has "ERalpha agonist activity and ERbeta antagonist activity," as recited in claims 1 and 13, it is respectfully pointed out that the recitations have not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.)

Regarding the methods of claims 7 and 8, Lobaccaro et al. teaches that the estrogen compounds can be used to treat estrogen-receptor containing mammary tumors, as discussed above, and renders obvious providing the compounds as recited in the claims, and thus teaches a method of treating estrogen deficiency disorders (i.e. tumors that can be treated by providing an estrogen, and thus are "estrogen deficient") by providing a therapeutic amount of the compound and inducing either ERalpha agonist or ERbeta antagonist activity, as recited in the claims. It is furthermore noted

that that the agonist and/or antagonist activity of a compound is a property thereof, and a product and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Accordingly, the composition and method rendered obvious by the references would, absent evidence to the contrary, meet the limitations pertaining to the ERalpha and ERbeta agonist or antagonist activity used therein.

It is furthermore noted that, as Lobaccaro et al. teaches that the compounds having affinity for the estrogen receptor, it would have been obvious to one of ordinary skill in the art to provide such compounds for the treatment of disorders resulting from the deficiency of such estrogenic compounds, as recited in claims 7 and 8, with the expectation that providing the estrogenic compound would reduce the estrogen deficiency.

Regarding claims 4 and 16, Lobaccaro et al. teaches providing the estradiol derivative that is a C4 homolog of the C5 compound as recited, and thus renders obvious providing the C5 compound as discussed above. Regarding claims 2 and 14, Lobaccaro et al. teaches providing a butene derivative of the estradiol that differs from the first structure as recited in claims 2 and 14 by only the presence of an extra methylene group. That is, Lobaccaro et al. teaches a C4 homolog of the compound having the side chain structure 1 shown in claims 2 and 14. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the compounds as recited in claims 2 and 14, with the

expectation of providing compounds having similar properties as those described by Lobaccaro et al.

Claims 1-2, 4, 7-8, 13-14 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article entitled "11Beat-Substituted Estradiol Derivatives. 2. Potential Carbon-11-Iodine-Labeled Probes for the Estrogen Receptor" by Napolitano et al, 1995 (of record.)

Napolitano et al. teaches 11Beta-substituted derivatives of estradiol including ethynyl and propynyl derivatives (see abstract, in particular.) Napolitano teaches that the compounds have high affinity for the estrogen receptor, and provides the affinities for compounds 3a (entry 5) having a propynyl group and entry 11 having an ethynyl group (see Table 1, in particular.) Napolitano et al. teaches that the length of the chain of the 1-alkynyl group at the 11beta position affects the binding affinity of the compounds, with the shorter chain having a great affinity (see page 2776, first full paragraph of conclusion section, in particular.) Napolitano et al. teaches that the compounds can be used as tumor-imaging radiopharmaceuticals (see first full paragraph of Introduction section, in particular), and thus teaches providing a pharmaceutical composition having the compounds, as recited in claim 1.

Napolitano et al. does not specifically teach the estrogenic compound having the group R_{11} that is a hydrocarbon group and that has a single linear chain having a length

of from 5 to 6 carbon atoms as the longest chain on carbon atom no. 11, as recited in claims 1, 8, and 13.

However, as the compounds 3a and entry 11 of Napolitano et al. differs from the instantly recited compounds by only an ethylene group (-CH2-CH2-), that is, Napolitano et al. teaches a C2 or C3 compound whereas the instant compounds are C5 or C6 compounds, it is considered that the instantly claimed compounds are homologous to the compound of Napolitano et al, and thus are expected to have similar properties to the compound as taught by Napolitano et al, such as estrogen receptor binding activity. Thus it is considered that one of ordinary skill in the art would have found it obvious to provide the C5 or C6 homologs of the Napolitano et al. C2 or C3 compound, with the expectation of providing a compound with similar properties. See *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977.)

Furthermore, as Napolitano et al. teaches that the length of the 11beta alkynyl side chain can effect the estrogen receptor binding affinity, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of length of the 11beta alkynyl side chain of the compound, according to the guidance provided by Napolitano et al, to provide a composition having desired properties, such as desired estrogen receptor binding affinities. It is noted that "[W]here the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, the pharmaceutical composition of claim 1, and the steroid compound of claim 13 are considered to be obvious over the teachings of Napolitano et al. Regarding the recitation the compound has "ERalpha agonist activity and ERbeta antagonist activity," as recited in claims 1 and 13, it is respectfully pointed out that the recitations have not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.)

Regarding the methods of claims 7 and 8, Napolitano et al. teaches that the estrogen compounds can be used as radiopharmaceuticals to image tumors, as discussed above, and renders obvious providing the compounds as recited in the claims. It is furthermore noted that Napolitano et al. teaches that the compounds have affinity for the estrogen receptor, and thus have estrogenic activity. Accordingly, it is considered that one of ordinary skill in the art would have been motivated to provide such compounds for the treatment of disorders resulting from the deficiency of such

estrogenic compounds, as recited in claims 7 and 8, with the expectation that providing the estrogenic compound would reduce the estrogen deficiency. It is furthermore noted that that the agonist and/or antagonist activity of a compound is a property thereof, and a product and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Accordingly, the composition and method rendered obvious by the references would, absent evidence to the contrary, meet the limitations pertaining to the ERalpha and ERbeta agonist or antagonist activity used therein.

Regarding claims 4 and 16, Napolitano et al. teaches providing the estradiol derivative that is a C2 or C3 homolog of the C5 compound as recited, and thus renders obvious providing the C5 compound as discussed above. Regarding claims 2 and 14, Lobaccaro et al. teaches providing a propynyl derivative of the estradiol that differs from the third structure as recited in claims 2 and 14 by only the presence of a extra methylene groups. That is, Napolitano et al. teaches a C3 homolog of the compound having the side chain structure 3 shown in claims 2 and 14. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the compounds as recited in claims 2 and 14, with the expectation of providing compounds having similar properties as those described by Napolitano et al.

Response to Arguments

Applicant's arguments filed July 13, 2006 have been fully considered but they are not persuasive.

Applicants point out that claims 2, 4, 14 and 16 were indicated as being allowable in the prior office action (although objected to as being dependent upon rejected claims), as showing unexpected results. Applicants assert that the claims have been amended to recite allowable subject matter as previously indicated by the Examiner. However, as discussed above, the indication of the allowability of these claims is being withdrawn upon further consideration of the "unexpected results" as set forth by Applicants.

In particular, Applicants refer to Table A and Table B to show that the compounds having the formula I with R11 comprising a single linear chain having a length of from 5 to 6 carbon atoms, exhibit unexpected results the ER-alpha and ER-beta receptor binding activity over those compounds having 4 or less carbon atoms. In particular, Applicants argue that the compounds having only 3 or 4 carbon atoms, such as the compound 1 or 2, act as agonists at both the ER-alpha and ER-beta receptor sites, whereas compounds having 5 carbon atoms, such as compound 5 or 6, act as an agonist at the ER-alpha site and an antagonist at the ER-beta site. Thus, Applicants argue that the compounds having 5 or 6 carbon atoms provide unexpected results in the

binding activity over those compounds having lower numbers of carbon atoms. However, the Examiner notes that this conclusion is not true for all compounds having lower numbers of carbon atoms. In particular, the Examiner draws attention to the compound 8 which is depicted in Table B as having a linear chain having a length of 3 carbon atoms that is substituted with a cyclopropyl group. Thus, this compound would be expected to exhibit a similar activity as those compounds that have the lower numbers of carbon atoms (C3 or C4). However, as shown in Table A, compound 8 actually exhibits agonist activity at the ER-alpha site and antagonist activity and the ER-beta site, and thus shows the activity that is asserted to be unique to only the compounds having longer linear chains of 5 to 6 carbon atoms. Accordingly, the mixed agonist and antagonist activity of the recited compounds having 5 to 6 carbon atoms is not considered to be unexpected over those compounds having shorter chains, because the compounds having the shorter chains are also capable of exhibiting the same type of estrogen receptor binding activities, as illustrated by compound 8 as shown by Applicants.

Furthermore, it is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). Applicant claims all compounds having the formula (I) that have the group R11 comprising a liner chain with 5 to 6 carbon atoms, and where, for example at least one of X or Y is an OH group. However,

Applicants show data only for those compounds having X as an OH group and Y as hydrogen, and where R11 has 5 carbon atoms, but not 6 carbon atoms. Accordingly, the showing of unexpected results is not commensurate with the scope of the claims.

Applicants further argue that Lobaccaro et al. and Napolitano et al dos not teach or suggest the specific derivatives having the length of 5 to 6 carbon atoms, and does not teach or suggest that they have both agonist and antagonist activity. However, as discussed above, Lobaccaro et al. and Napolitano et al. teach compounds that are homologous to those claimed, and thus provides motivation for providing the compounds with the expectation of similar properties, such as binding properties. Lobaccaro et al. and Napolitano et al. also teach that the length of the side chain can be adjusted to affect the binding affinity and properties, and thus provides motivation for varying and/or optimizing the chain length, as discussed above.

In response to applicant's argument that neither Lobaccaro et al. nor Napolitano et al. recognize that the compounds having both agonist and antagonist activity, it is noted that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985.)

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER